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Diastereoselective Rhodium-Catalyzed Ene-Cycloisomerization Reactions of Alkenylidenecyclopropanes: Total Synthesis of (−)-α-Kainic Acid

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Supporting Information

ABSTRACT: The rhodium-catalyzed ene-cycloisomerization of alkenylidenecyclopropanes provides an atom-economical approach to five-membered carbo- and heterocycles that contain two new stereogenic centers. A key and striking feature of this protocol is that the alkene geometry does not impact the efficiency and diastereocontrol, which provides excellent synthetic versatility. For instance, (*E*)- and (*Z*)-allylic alcohols furnish the corresponding aldehydes with similar efficiency and selectivity. This process facilitates the construction of a key intermediate in an eight-step total synthesis of (−)-α-kainic acid.

Transition-metal-catalyzed ene-cycloisomerization reactions represent an important class of reactions due to their ability to construct cyclic scaffolds with a high degree of molecular complexity in an atom-economical fashion.[1] In this context, the ene-cycloisomerization of 1,6-dienes has not been extensively examined in comparison with the analogous process involving 1,6-enynes, which may be attributed to the low reactivity of alkenes with unsaturated transition-metal complexes.[1−3] Nevertheless, both substrates provide the same type of product, which has a new stereogenic center and an exocyclic alkene. In a program directed toward the development of metal-catalyzed carbocyclization reactions, we have recently described the merit of alkenylidenecyclopropanes (ACPs) in the context of a rhodium-catalyzed [(3+2)+2] carbocyclization reaction with activated alkynes for the diastereoselective construction of bicycloheptadienes.[4] We envisioned that the omission of the exogenous 2π component, namely, the alkyne, would promote β-hydride elimination of the intermediary metallacycle to facilitate the construction of highly functionalized five-membered rings with two new stereogenic centers and an array of functionality, namely, aldehydes and alkenes.[5,6] Herein, we now describe the metal-catalyzed ene-cycloisomerization of ACPs **1** for the stereoselective construction of the five-membered carbo- and heterocyclic aldehydes **2** and dienes **3** (Scheme 1).

Table 1 summarizes the preliminary studies to determine the feasibility of this transformation using ACP **1a** (X = O, R = H). Treatment of (*Z*)-**1a** (Y = CH_2OH, Z = H) with $[Rh(COD)Cl]_2$ modified with triphenyl phosphite in acetonitrile at 60 °C furnished only a trace of **2a**, albeit with excellent diastereoselectivity (entry 1). We envisioned that variations in solvent, temperature, and catalyst would provide further improvements in efficiency, since the conversion mirrored the yield. Although changing the solvent from acetonitrile to tetrahydrofuran (THF) and then to toluene provided modest improvements in the yield (entries 2 and 3 vs entry 1), increasing the reaction temperature proved critical for driving this reaction to completion (entry 4 vs 3). Additional studies illustrated that minor modifications of the ligand further improved the efficiency (entry 5 vs 4).[7] The next phase of the study focused on the impact of the olefin geometry on this reaction, since related rhodium-catalyzed reactions with 1,6-enynes are particularly sensitive to the alkene geometry. For example, the *E* isomers are particularly poor substrates for this transformation.[3a] Treatment of (*E*)-**1a** under the optimal conditions furnished **2a** with analogous reactivity and selectivity (entry 6 vs 5). Additionally, the fact that the two geometries provide the same diastereoisomer with similar efficiencies simplifies the preparation of the alkene precursors, since they do not have to be stereodefined, thereby making this a more convenient process for synthetic applications.

Scheme 1. Rhodium-Catalyzed Ene-Cycloisomerization of ACPs for the Construction of Functionalized Five-Membered Carbo- and Heterocycles

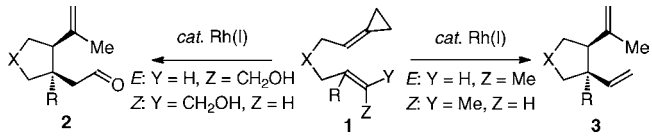

Table 2 outlines the application of the optimized reaction conditions (Table 1, entries 5 and 6) to a range of carbon- and heteroatom-tethered ACPs to demonstrate the synthetic scope of this novel transformation. Interestingly, the diastereoselectivity and efficiency of this process is independent of the nature of the ACP tether, alkene geometry and substitution, which provides outstanding versatility. For example, the ene-cycloisomerizations of carbon- (entries 9−12) and heteroatom-tethered (entries 1−8) ACPs with allylic alcohol and 1,2-disubstituted alkene substitutents provide aldehydes **2** and dienes **3**, respectively, with analogous efficiencies and selectivities (entries 1/2, 5/6, 9/10 vs 3/4, 7/8, 11/12). Additionally, the cycloisomerization of trisubstituted alkenes provides products with quaternary carbon stereogenic centers (entries 2, 4, 6, 8, 10, and 12), which further demonstrates the

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Table 1. Optimization of the Ene-Cycloisomerization of ACPs (Scheme 1; 1a, X = O, R = H)[a]

	ACP **1a**						
entry	Y	Z	ligand	temp (°C)	solvent	yield (%)[b]	*ds* **2a**[c]
1	CH_2OH	H	$P(OPh)_3$	60	MeCN	3	≥19:1
2	CH_2OH	H	$P(OPh)_3$	60	THF	17	≥19:1
3	CH_2OH	H	$P(OPh)_3$	60	PhMe	21	≥19:1
4	CH_2OH	H	$P(OPh)_3$	100	PhMe	89	≥19:1
5	CH_2OH	H	$P(OTol)_3$	100	PhMe	99	≥19:1
6	H	CH_2OH	$P(OTol)_3$	100	PhMe	99	≥19:1

[a]All reactions were carried out on a 0.25 mmol reaction scale (0.05 M) utilizing $[Rh(COD)Cl]_2$ (4 mol %) modified with the triaryl phosphite (16 mol %). [b]GC yields. [c]Ratios of diastereoisomers were determined by 500 MHz ^1H NMR analyses of the crude reaction mixtures.

Table 2. Scope of the Diastereoselective Rhodium-Catalyzed Ene-Cycloisomerization of ACPs (Scheme 1)[a]

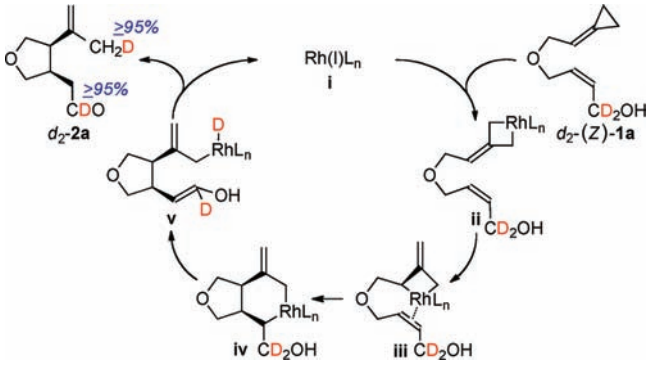
	ACP **1**							
entry	X	R	Y	Z	*E*/*Z*		yield (%)[b]	*ds* **2**/**3**[c]
1	O	H	CH_2OH	H	*Z*	**2a**	97	≥19:1
2	O	Me	H	CH_2OH	*E*	**2b**	93	≥19:1
3	O	H	H	Me	*E*	**3c**	80	≥19:1
4	O	Me	H	Me	*E*	**3d**	89	≥19:1
5	NTs	H	CH_2OH	H	*Z*	**2e**	81	≥19:1
6	NTs	Me	H	CH_2OH	*E*	**2f**	80	≥19:1
7	NTs	H	H	Me	*E*	**3g**	92	≥19:1
8	NTs	Me	H	Me	*E*	**3h**	84	≥19:1
9	$C(CO_2Me)_2$	H	CH_2OH	H	*Z*	**2i**	89	≥19:1
10	$C(CO_2Me)_2$	Me	H	CH_2OH	*E*	**2j**	80	≥19:1
11	$C(CO_2Me)_2$	H	H	Me	*E*	**3k**	96	≥19:1
12	$C(CO_2Me)_2$	Me	H	Me	*E*	**3l**	93	≥19:1

[a]All reactions were carried out on a 0.25 mmol reaction scale using $[Rh(COD)Cl]_2$ (4 mol %) modified with tri-*p*-tolyl phosphite (16 mol %) in toluene at 100 °C (0.05 M). [b]Isolated yields. [c]Determined by 500 MHz ^1H NMR analyses of the crude reaction mixtures.

synthetic utility of this process for target-directed synthesis. *Overall, this work provides diastereoselective access to functionalized five-membered carbo- and heterocyclic rings, which are present in an array of important bioactive agents.*

Scheme 2 provides support for the proposed catalytic cycle for this ene-cycloisomerization. Treatment of the ACP d_2-(*Z*)-**1a** under the optimized reaction conditions provided the aldehyde d_2-**2a** in 93% yield, which is consistent with a type-I process involving the formation of a metallacycle intermediate.[1b] For example, oxidative addition of **i** into the distal bond of ACP d_2-(*Z*)-**1a** presumably generates the metallacyclobutene **ii**, which undergoes rearrangement to afford **iii**.[8] Stereoselective carbometalation of the alkene provides the cis-fused metallacycle **iv** (or the η^3-allyl intermediate), which can undergo selective β-hydride elimination at the terminal position to afford the metal deuteride/enol **v**.[5,9] Tautomerization of **v** and concomitant reductive elimination provides the aldehyde d_2-**2a** with ≥95% incorporation of the deuterium in the aldehyde and β-isopropenyl groups.

Scheme 2. Proposed Catalytic Cycle for the Diastereoselective Rhodium-Catalyzed Ene-Cycloisomerization Reaction



To showcase the synthetic utility of this new transformation, we elected to devise a concise total synthesis of (−)-α-kainic acid (**9**), a member of the kainoid family of natural products, which are structurally related non-proteinogenic amino acids.[10] Kainic acid was isolated in 1953 from the Japanese marine algae *Digenea simplex* and exhibits potent anthelmintic and neuroexcitatory activity, making it a biologically important target.[11] Moreover, it has an estimated market value of $1 billion per annum,[12] which provides the impetus for the development of a practical synthesis of this agent.[13] We envisioned that the distinctive *anti,syn*-2,3,4-trisubstituted pyrrolidine ring could be installed with a diastereoselective rhodium-catalyzed ene-cycloisomerization reaction, using the C2 substituent to direct the diastereoselectivity in a manner analogous to that for 1,6-enynes.

The synthesis of **9** commenced with a one-pot sequential oxidation/homologation reaction (Scheme 3). Dess−Martin oxidation of commercially available amino alcohol **4** followed by a concomitant Wittig homologation furnished the conjugated ester in 77% yield.[14] Palladium-catalyzed allylic amination of 1-vinylcyclopropyl tosylate afforded **5** in 84% yield.[15] Interestingly, the order of the reactions in this sequence was important to reduce epimerization of the C2 substituent.[13c] DIBAL-H reduction of the α,β-unsaturated ester **5** in the presence of $BF_3{\cdot}OEt$[16] afforded allylic alcohol **6**, which set the

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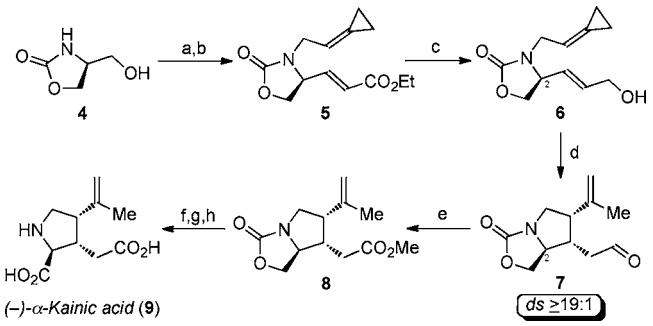
Scheme 3. Asymmetric Total Synthesis of (−)-α-Kainic Acid Using a Rhodium-Catalyzed Ene-Cycloisomerization of an Alkenylidenecyclopropane[a]



[a]Reagents: (a) DMP, pyridine, Ph_3PCHCO_2Et, DCM/MeCN, 40 °C, 77%. (b) 1-Vinylcyclopropyl tosylate, cat. $Pd(PPh_3)_4$, THF, then pronucleophile, NaH, THF, RT, 84%. (c) DIBAL-H, BF_3·OEt, DCM, −78 °C to RT, 70%. (d) $[Rh(COD)Cl]_2$ (4 mol %), tri-*p*-tolyl phosphite (24 mol %), THF, 135 °C (sealed tube), 69%. (e) PDC, DMF, MeOH, RT, 73%. (f) NaOMe, MeOH, 0 °C to RT, 83%. (g) Jones reagent (8 N), acetone, 0 °C to RT. (h) LiOH, $^{i}PrOH/H_2O$, 120 °C then H^+ (Dowex-50WX8), 85% over two steps.

stage to examine the key rhodium-catalyzed ene-cycloisomerization reaction. Treatment of **6** with the rhodium complex derived from $[Rh(COD)Cl]_2$ modified with tri-*p*-tolyl phosphite in THF at 135 °C furnished the key *anti,syn*-2,3,4-trisubstituted pyrrolidine skeleton **7** in good yield with excellent diastereocontrol (*ds* ≥19:1).[17] Interestingly, the optimized reaction conditions utilized in Table 2 resulted in a lower yield and significantly lower diastereoselectivity for the formation of **7** (*ds* = 4:1), which will be the subject of further investigation. Oxidation of the aldehyde using a modified Corey procedure furnished the known methyl ester **8** in 73% yield.[18] Although this constitutes a formal synthesis of kainic acid, we elected to convert the methyl ester to the natural product **9** using a modified sequence that was originally developed by Montgomery and co-workers.[13c] Sodium methoxide-mediated ring opening of the carbamate followed by oxidation of the primary alcohol to the carboxylic acid and concomitant global deprotection furnished **9** in 71% overall yield from **8**. Hence, the total synthesis of (−)-α-kainic acid (**9**) was accomplished in eight steps from commercially available amino alcohol **4** in 17% overall yield. Notably, this strategy provides a synthesis that constructs the fully functionalized skeleton with loss of only methanol, ethanol, and carbon dioxide, which makes this a particularly atom-economical synthesis of this important agent. Finally, this total synthesis represents one of the most concise and efficient developed to date, which may be suitable for commercialization.

In conclusion, we have developed a highly diastereoselective rhodium-catalyzed ene-cycloisomerization reaction of carbon- and heteroatom-tethered ACPs. This protocol provides the same diastereoisomer with similar efficiency irrespective of the alkene geometry, which simplifies the preparation of the alkene precursor. The synthetic utility of this approach was highlighted in the concise eight-step total synthesis of (−)-α-kainic acid (**9**) in 17% overall yield. Hence, we envision that this methodology will provide a convenient atom-economical approach to an array of five-membered carbo- and heterocyclic structures in the context of target-directed synthetic applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for all new compounds, including NOE data and CIF files for **3g** and derivatives of **2e** and **2f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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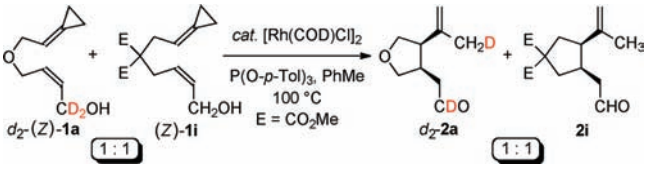
(7) Interestingly, bidentate phosphine ligands also provide excellent results in this reaction. For example, the analogous process using dppp (8 mol %) as the ligand furnished ene-cycloisomerization product **2a** in 95% yield with ≥19:1 diastereoselectivity.

(8) The direct oxidative rearrangement of Rh(I)L_n with d_2-(*Z*)-**1a** to provide intermediate **iii** is an alternative pathway to this intermediate.

(9) Although we envisioned the intramolecular transfer of the deuterium to the *β*-isopropenyl group (Scheme 2), the crossover experiment outlined below confirmed this assumption. Treatment of a 1:1 mixture of d_2-(*Z*)-**1a** and (*Z*)-**1i** under the optimal conditions furnished d_2-**2a** and **2i** without deuterium scrambling in yields of 83 and 82%, respectively.



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